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# The Transition State and Cognate Concepts

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## Contents

1. Introduction
2. Conceptual power of the transition state
3. Glossary of Terms
  - 3.1 Potential-energy surface (PES)
  - 3.2 Saddle point
  - 3.3 Minimum energy reaction path
  - 3.4 Reaction coordinate (part 1)
  - 3.5 Activated complex
  - 3.6 Transition structure
  - 3.7 Intrinsic reaction coordinate
  - 3.8 Transition vector
  - 3.9 Transition-state structure
  - 3.10 Transition state
4. Computation and experiment for simple systems
  - 4.1 Application of statistical mechanics to a single transition structure
  - 4.2 Kinetic isotope effects: transition structure vs. transition-state structure
  - 4.3 Complications: saddle points in series and in parallel - virtual transition states
  - 4.4 Potential energy vs. free energy
5. Transition state for condensed systems: concepts and simulations
  - 5.1 Free energy surfaces
  - 5.2 Collective variables
  - 5.3 Minimum free energy paths
  - 5.4 Variational TST
  - 5.5 Transmission coefficient
  - 5.6 Reaction coordinate (part 2)
  - 5.7 The equicommititor and the error in TST
6. Concluding remarks

## Acknowledgments

## References

## Abstract

This review aims firstly to clarify the meanings of key terms and concepts associated with the idea of the transition state, as developed by theoreticians and applied by experimentalists, and secondly to provide an update to the meaning and significance of the transition state in an era when computational simulation, in which complexity is being increasingly incorporated, is commonly employed as a means by which to bridge the realms of theory and experiment. The relationship between the transition state and the potential-energy surface for an elementary reaction is explored, with discussion of the following terms: saddle point, minimum-energy reaction path, reaction coordinate, activated complex, transition structure, intrinsic reaction coordinate, transition vector, transition-state structure, and transition state. Structural information determined by the application of computational methods to simple systems or inferred from empirical studies is critically discussed in the light of various complications. Consequently, the relationship between the transition state and the free-energy surface for an elementary reaction within a condensed system is explored, with discussion of collective variables, minimum free-energy paths, variational transition-state theory, transmission coefficients, more about reaction coordinates, and equicommititors. It is noted that any visual picture of a transition state is necessarily an average view, and an updated definition of the transition state is proposed.

## Keywords

Computational simulation; dividing surface; equicommititor; free-energy surface; potential-energy surface; reaction coordinate; transition state

## 1. INTRODUCTION

The transition state has been a cornerstone of physical organic chemistry for as long as the latter has been recognised as a sub-discipline. In his highly influential 1940 book *Physical Organic Chemistry*,<sup>1</sup> Hammett not only provided a description of transition-state theory (TST), but also argued its consistency with the Brønsted rate equation, recognised its connection to rate-equilibrium relationships, and gave example schematic structures for transition states in enolization of acetophenone and semicarbazone formation.

The historical and conceptual development of TST, almost simultaneously by Eyring<sup>2</sup> and by Evans and Polanyi<sup>3</sup> in 1935, has been discussed by (among others) Laidler and King<sup>4</sup>, who argued that the genius of this work was that it brought together three essential features, none of which was novel, and proposed a simple but general rate equation. These were that: (i) rates can be calculated by focusing attention on the saddle point of the potential-energy surface (PES) describing a chemical reaction; (ii) the transition state is in quasi-equilibrium with the reactants; (iii) motion in the transition state along a particular "reaction coordinate" can be treated as a free translational motion and expressed by using kinetic theory. The significance of the saddle point for understanding the reaction rate had been recognised by Pelzer and Wigner<sup>5</sup> (working in Polanyi's group in Berlin) based upon Eyring and Polanyi's 1931 semi-empirical theoretical PES (Fig. 1a) for the collinear  $\text{H} + \text{H}_2 \rightarrow \text{H}_2 + \text{H}$  reaction,<sup>6</sup> whereas the particular significance of 'the normal coordinate corresponding to passing over the barrier' in the transition state (*i.e.* the reaction coordinate) was noted by Eyring.<sup>2</sup>

This chapter consistently employs the terms transition state and TST, rather than "activated complex" and "theory of absolute reaction rate" (or "absolute rate theory") as originally coined by Eyring,<sup>2,7</sup> in order to reflect predominant current usage. However, these terms can cause confusion, and the literature contains many examples of their abuse. One purpose of this article is to clarify the meanings of these and associated terms and concepts. Furthermore, recent years have seen an explosive increase in computer simulations of chemical reactions, especially for condensed-phase systems, and this has brought to light some issues that were perhaps not apparent when TST was applied only to relatively simple systems. Accordingly, the second purpose of this article is to provide an update to the meaning and significance of the transition state in an era when computational simulation is commonly employed as a means by which to bridge the realms of theory and experiment. It is not the purpose of this chapter to review TST *per se*: there are many thorough and excellent treatments of the assumptions and derivations of TST, including the textbooks on chemical kinetics by Smith<sup>8</sup> and by Steinfeld, Francisco and Hase.<sup>9</sup> As implied by its title, the aim of this contribution is to focus upon the concept of the transition state itself in regard to both theory and experiment, and particularly in the light of relatively recent developments in computational simulations of chemical reactions.

## 2. CONCEPTUAL POWER OF THE TRANSITION STATE

The scope of the newly developed TST was greater than the ability of its early practitioners to generate reliable PESs for any but the very simplest of chemical reactions using quantum-mechanical methods, and these quantitative inadequacies were fully apparent to those involved. At the 1937 Faraday Society meeting<sup>10</sup> in Manchester on 'Reaction Kinetics' in, Moelwyn-Hughes<sup>11</sup> pointed out that TST was seriously limited by the fact that chemists were interested in systems for which partition functions were not available, and Polanyi remarked that he attached 'no importance ... to a precise numerical agreement between theory and experiments, but believe that the theory can claim to give a reasonable picture of the mechanism of chemical reactions which would otherwise remain in the dark.'<sup>12</sup> Hammett commented that it was 'most important to distinguish the very valuable qualitative and conceptual accomplishments of these new theories from the quantitative inadequacies which they may still possess.'<sup>13</sup> Furthermore, in emphasizing that the Brønsted and Hammett equations were linear free-energy relationships, he asserted: 'I have already indicated that these linear relations have a considerable practical value for the diagnosis of reaction mechanisms and for the prediction of reaction rates and equilibria. On the theoretical side their existence carries a number of important implications. Thus the complete interchangeability of equilibrium and rate constants is one of the simplest and perhaps one of the strongest supports of the transition-state theory of reaction rates because it demonstrates an otherwise inexplicable identity between the ways in which composition and structure of reactant affect equilibria and rates respectively.'<sup>14</sup>

The idea of a transition state whose properties were responsible for (and in some way could be related to) the observed kinetic behaviour of organic reactions in solution was immediately appealing to leading experimentalists in the area of kinetics and mechanisms of chemical reactions. The first mention of "transition state" in the chemical literature, other than by Polanyi's group, appears to be a paper (submitted in December 1935) by Hughes, Ingold and Shapiro<sup>15</sup> concerning mechanisms of aliphatic nucleophilic substitution. Their discussion of mechanistic change (from  $S_N2$  to  $S_N1$ ) in response to structural change was accompanied by a diagram (Fig. 1b) to illustrate 'an imaginary potential energy surface ... which we assume to possess not only the two reactant valleys A and B usual for a gas reaction with a transition state at T, but also a third valley at C due to ion solvation) together with the included pair of ridges DEF.' The resemblance between this schematic representation and the laboriously hand-calculated quantum-mechanical PES of Eyring and Polanyi<sup>6</sup> is striking. The (semi-)quantitative TST description has inspired a very powerful conceptual tool for qualitative mechanistic reasoning. The idea of the transition state had captured the imagination of (enlightened) experimental chemists, and it was not long before organic reaction mechanisms and transition states were inextricably linked: e.g. 'most discussions of the mechanism of organic reactions are thus presented in terms of the transition-state theory. Indeed, the attempt to find a mechanism for a given reaction is essentially a matter of defining the one or more transition states between the starting materials and the products.'<sup>16</sup> At the 1941 meeting of the Faraday Society in London on '*Mechanism and Chemical Kinetics of Organic Reactions in Liquid Systems*', Ingold observed 'the profound effect of [the 1937 Discussion in Manchester] on the present papers, for instance, in the numerous applications which are made of the transition state theory, the usefulness of which was much emphasised in the earlier meeting.'<sup>17</sup>

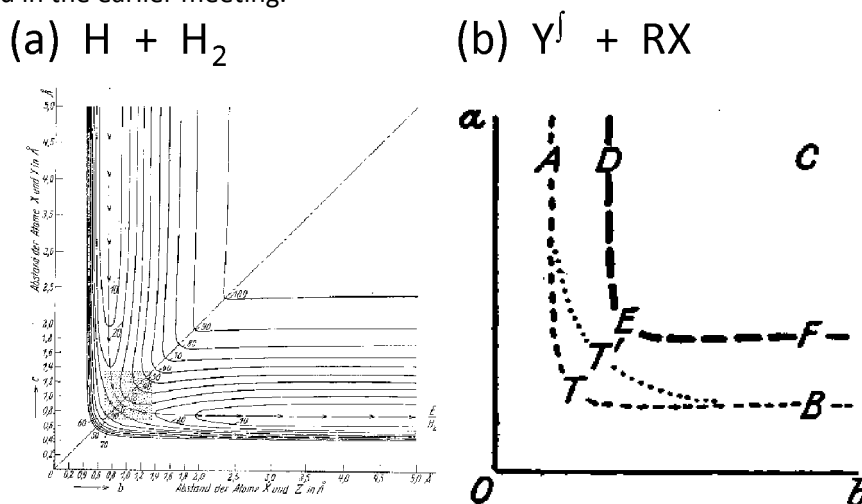


Fig. 1 (a) Quantum-mechanically calculated potential-energy surface (1931) for the collinear  $H + H_2$  reaction (ref. 6; image reproduced from Nye MJ. *J Comput Chem* 2007;28:98-108 with permission from Wiley). (b) Schematic representation of an imaginary potential-energy surface (1936) for aliphatic nucleophilic substitution (from ref. 15, reproduced with permission from the Royal Society of Chemistry).

### 3. GLOSSARY OF TERMS

#### 3.1 Potential-energy surface (PES)

Within the Born-Oppenheimer approximation, the smoothly varying potential energy for a particular electronic state (usually the ground state, unless specifically stated otherwise) of a system of atoms can be represented as function of the coordinates that define the positions of the nuclei in configuration space. For a very simple system (e.g. a collinear triatomic) only two coordinates are required to describe the potential energy: thus a complete PES (Fig. 1a) can be plotted as a function of two distances, namely those between the central H atom and each of the two terminal H atoms, in the collinear  $H + H_2$  system studied

by Eyring and Polanyi.<sup>6</sup> For any system requiring more than two coordinates in order to define completely the relative positions of all of its atoms (*i.e.* for every real system capable of undergoing a chemical reaction), the potential energy is a function of all of the internal coordinates and is represented by a hypersurface in multidimensional space. A system of  $N$  atoms has  $n = 3N - 6$  internal degrees of freedom and requires this number of coordinates to specify its geometry completely; being independent of its translational position or rotational orientation in  $3N$ -dimensional space, it is convenient to express the potential energy as a function of a complete set of  $n$  non-redundant internal coordinates  $\{q_1, q_2, \dots, q_n\}$ . However, even a triatomic system without the constraint of collinearity involves too many coordinates for its potential-energy hypersurface to be readily visualized. It is common practice, therefore, to display a PE hypersurface as a PES of reduced dimensionality, usually by plotting the potential energy as a function of only two coordinates, with the assumption that the energy at each point on the resulting PES is minimized with respect to variation in all the other  $n - 2$  degrees of freedom of a non-linear polyatomic system. Care should be exercised in the use of a reduced-dimensionality PES to describe the reactive behavior of a molecular system which also involves conformational change: whereas the complete hypersurface includes every geometrically distinct species (*i.e.* all conformers), the reduced PES may oversimplify the system.

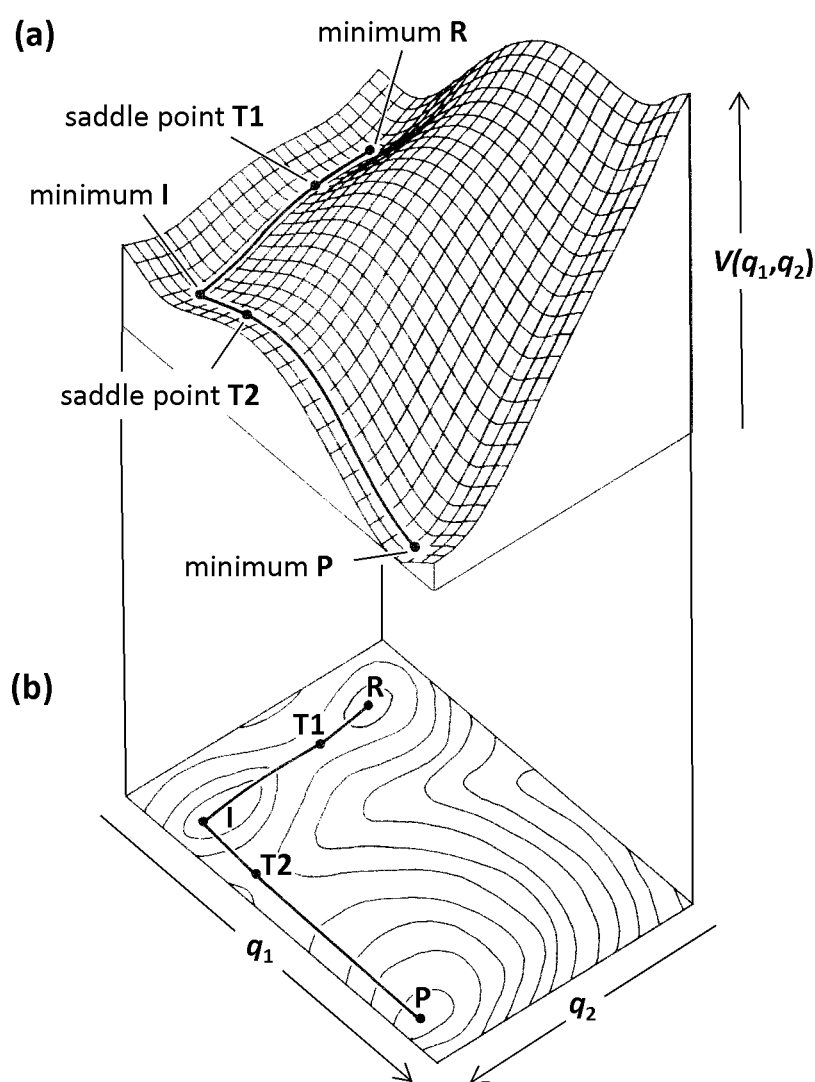


Fig. 2 (a) 3D representation of a PES with  $V(q_1, q_2)$  plotted as a function of two internal coordinates  $q_1$  and  $q_2$ . (b) 2D Iso-potential contour map obtained by projection of the PES onto the base plane defined by  $q_1$  and  $q_2$ . Adapted from Ref. 18, with permission from Springer Nature.

### 3.2 Saddle point

Fig. 2 shows (a) a 3D PES of reduced dimensionality plotted as a function of two internal coordinates ( $q_1$  and  $q_2$ ) together with (b) the corresponding 2D iso-potential energy contour map obtained by projection of the PES onto the base plane defined by  $q_1$  and  $q_2$ .<sup>18</sup> Both the surface and the map contain five stationary points, at which the gradient of the potential energy with respect to each of the coordinates is zero: there are three minima (**R**, **I** and **P**) and two saddle points (**T1** and **T2**). Each of the minima (corresponding to reactants, intermediate, and products) are characterized by positive curvature along both principal axes of curvature, whereas each of the saddle points (corresponding to transition states) possesses one principal axis with negative curvature and one with positive curvature. The geometry at each of the stationary points (denoted by a solid circle on Fig. 2) is independent of the particular choice of the coordinates  $q_1$  and  $q_2$ . Stationary points **T1** and **T2** are both first-order saddle points, as they have one and only one principal axis with negative curvature, meaning that the Hessian matrix of second derivatives of  $V$  with respect to  $q_1$  and  $q_2$  has one negative eigenvalue, corresponding to an imaginary harmonic vibrational frequency.<sup>19</sup> A stationary point whose Hessian has two negative eigenvalues is a second-order saddle point, denoting a local potential-energy maximum.

### 3.3 Minimum energy reaction path

The solid black line shown on the iso-potential-energy contour map (Fig. 2b) as connecting the stationary points **R**, **T1**, **I**, **T2** and **P** delineates a minimum energy reaction path (MERP). Note that (in this example) it is a path in the 2D configuration space of the coordinates  $q_1$  and  $q_2$ ; it is not the 3D path over the PES itself, for which the third dimension is energy. The MERP intersects each of the energy contours at right angles; it is an orthogonal trajectory,<sup>20</sup> corresponding to the path of steepest descent from a saddle point. However, in general, the shape of the MERP depends on the particular choice of coordinates  $q_1$  and  $q_2$ , since the transformations between different sets of coordinates (which may include arbitrary subsets of all possible bond distances, bond angles and dihedral angles) are not generally orthogonal, *i.e.* they do not necessarily preserve the values of all distances and angles. The fact of the coordinate-dependency of the shape of the MERP is not widely recognized but explains why some authors have suggested that, strictly speaking, the prefix "pseudo" should be employed with the term MERP.<sup>18</sup> In practice the prefix is almost never used, but it should still be borne in mind that a MERP obtained in this way does not represent a physical reaction path. Furthermore, MERPs generated for the same set of stationary structures but using different choices of coordinates are not physically equivalent.<sup>18</sup> This important point may be better understood by considering two MERPs, generated using two different sets of internal coordinates but connecting the same pair of adjacent stationary structures: the sequence of structures along each of the two MERPs (perhaps transformed into Cartesian coordinates and displayed as a movie) would not be the same, although in each case the starting point and the finishing point would be the same structure.

Since the MERP is the union of the two paths of steepest descent in opposite directions away from the saddle point, the saddle point itself is necessarily located at the highest-energy point on the lowest-energy path interconnecting the reactant and product energy minima for an elementary reaction. There are an infinite number of paths between any pair of adjacent minima, but the only one that satisfies this condition is a MERP passing through the saddle point.

### 3.4 Reaction coordinate (part 1)

Progress along a MERP is measured by the value of a parameter called the reaction coordinate. Mezey has pointed out that, while the terms "reaction path" and "reaction coordinate" are frequently used interchangeably, a path is a geometrical object whereas a coordinate is a numerical measure.<sup>21</sup> The path itself is a function of all of the internal coordinates, and in general it is not possible to identify any single one of these coordinates as the reaction coordinate. A plot of potential energy as a function of the (numerical value of the) reaction coordinate is called sometimes a "reaction-coordinate diagram"<sup>22</sup> and sometimes a "potential energy profile".<sup>23</sup> Neither term is satisfactory: the former fails to mention that the diagram is an energy profile, whereas the latter ignores the fact that an infinite number of profiles can be obtained as cross-sections of any PES. A better name would be "reaction profile of minimum-energy".

Since a reaction coordinate is obtained from a MERP, which in turn requires the location of a saddle point in configuration space to be known, a reaction coordinate cannot be used in order to find a saddle point. However, it is common to see the term being misunderstood in such a manner. Typically one of the

coordinates of the reactants, the value of which must change significantly, smoothly and monotonically between reactant and product geometries, is selected as an independent variable; this variable is incremented between its reactant and product values, and at each value the potential energy is minimized with respect to all the remaining  $n - 1$  internal coordinates. Since, as noted above, the reaction coordinate is a function of all  $n$  coordinates, it would be extraordinary if this were equivalent to the single coordinate selected as the independent variable. The independent variable is sometimes called the "distinguished coordinate".<sup>24</sup>

It is worth noting that a reaction path obtained by constrained energy minimization at successive values of a distinguished coordinate is not guaranteed to pass through a saddle point. It does so only if the resulting potential–energy profile is smooth and continuous. The presence of a discontinuity in the profile is evidence that the path is also discontinuous and does not pass through the saddle point. Such discontinuities are often masked by a "join-the-dots" presentation of the discrete energies for the incremented independent variable, which appears to show a continuous curve, but with a dramatic change in the magnitude of its slope on either side of the apparent maximum in the energy profile.<sup>24</sup>

### 3.5 Activated complex

Eyring originally used the term "activated complex" for the configuration of atoms at the saddle point on a PES.<sup>2,7</sup> The term was and is synonymous with "transition state" as defined by Evans and Polanyi,<sup>3</sup> although it is possible to make a clear distinction between an assembly of atoms with specified coordinates in configurational space and the thermodynamic state of that assembly. For example, Frost and Pearson wrote that 'a system *in* the transition state is called an activated complex',<sup>25</sup> Gould's textbook on organic mechanisms suggested that 'a molecule or group of molecules passing *through* the transition state is said to be an activated complex'<sup>26</sup> and Smith considered a molecular system near to the saddle point '*to be in* the transition state or *to be an* activated complex'<sup>18</sup> (our italics in each of these quotes). Steinfeld, Francisco and Hase chose to avoid using the term activated complex for two reasons: firstly because "complex" implies an entity which has a chemically significant lifetime, which the transition state does not have, and secondly because the same term is often used for the collision complex in molecular beam experiments, which is something different.<sup>9</sup> The 1994 *IUPAC Glossary of Terms Used in Physical Organic Chemistry* defined a "complex" as a molecular entity formed by loose association involving two or more component molecular entities;<sup>23</sup> an activated complex fails this definition since its chief characteristics are its transience and instability with respect to the reactants/products of an elementary chemical reaction.

### 3.6 Transition structure

The configuration of atoms at the saddle point on a PES is a transition structure. This term appears to have been first used in this sense by Komornicki, Dykstra, Vincent and Radom,<sup>27</sup> without definition, but was popularized by Schlegel.<sup>28</sup> It is a molecular entity which has zero forces within its internal degrees of freedom and which possesses a single imaginary vibrational frequency. In computational explorations of stationary structures on PESs, it is very useful to use this term to refer to a molecular structure corresponding to a saddle point, which has a specific geometry and energy. It is also useful to distinguish a transition structure from a transition state, since the latter should not be considered as a single and specific molecular structure, for reasons explained below.

### 3.7 Intrinsic reaction coordinate

The MERP in mass-weighted Cartesian coordinates between the transition structure of an elementary reaction and its reactants and products is usually called the intrinsic reaction coordinate (IRC),<sup>20,29</sup> although strictly speaking it should be the intrinsic reaction path (IRP).<sup>21</sup> From a physical point of view, it may be considered as an imaginary relaxation path along which the molecular system glides from a saddle point down to either of the two adjacent minima, with continuous dissipation of energy, but almost infinitely slow motion,<sup>30</sup> and without vibration or rotation.<sup>29</sup> An "IRC calculation" is now a standard technique in computational chemistry for verifying that a saddle point interconnects a specific pair of energy minima on a PES.<sup>31</sup> The numerical value of the IRC at any point along the IRP is usually taken to be zero at the saddle point, positive in the direction of the products, and negative in the direction of the reactants; because it is evaluated in mass-weighted coordinates and using atomic units, the output from most computer codes presents the value of the IRC as a dimensionless quantity  $s/\text{amu}^{1/2} \text{ bohr}$ . Note that this special case of a

MERP does not suffer the coordinate-dependency noted above for a MERP generated using an arbitrary choice of internal coordinates: this is because it is defined in terms of Cartesian coordinates, and because the mass-weighting takes account of the dynamical character of the system, albeit classically and at 0 K.

### 3.8 Transition vector

As originally defined, the transition vector is the eigenvector of the Hessian matrix (the second derivatives of potential energy with respect to displacements in the internal coordinates) corresponding to the single negative eigenvalue at a first-order saddle point.<sup>32</sup> However, since computational characterization of a saddle point on the PES for an elementary reaction is usually achieved by performing a vibrational analysis upon the transition structure in mass-weighted Cartesian coordinates, the resulting eigenvectors are actually the normal modes of vibration, and the one corresponding to the single imaginary vibrational frequency is usually identified as the transition vector, which is sometimes also called the reaction-coordinate vibrational mode. (It has also been called the "transition coordinate",<sup>23</sup> but this term should be avoided as it has been defined with a different meaning for protein folding.<sup>33</sup>) Infinitesimal motion along the transition vector determines the initial direction, leading toward either reactants or products, of the intrinsic reaction coordinate (IRC); it is therefore tangential to the IRC at the saddle point.

### 3.9 Transition-state structure

"Transition-state structure" is not synonymous with "transition structure". The latter refers to the molecular structure corresponding to a saddle point on a PES, and is thus an inherently theoretical entity which is determined by the methods of computational chemistry. The former term refers to the structure that may be inferred for the transition state of a chemical reaction by means of the application of (usually indirect) experimental techniques. TST has proved itself to be extraordinarily useful as an interpretative tool for results obtained from chemical kinetics experiments, including enthalpies, entropies and volumes of activation, linear free-energy relationships, and kinetic isotope effects. Many examples of the transition-state structures derived by these experimental methods have been discussed in the excellent volume edited by Gandour and Schowen.<sup>34</sup>

### 3.10 Transition state

The reader might be a little surprised that it is only at this point in the chapter that a definition of the term "transition-state" is considered. The original 1979 *Glossary of Terms Used in Physical Organic Chemistry* contained the following entry for "transition state".<sup>35</sup>

*In theories describing elementary reactions it is usually assumed that there is a transition state of more positive molar Gibbs energy between the reactants and the products through which an assembly of atoms (initially composing the molecular entities of the reactants) must pass on going from reactants to products in either direction. In the formalism of "transition state theory" the transition state of an elementary reaction is that set of states (each characterized by its own geometry and energy) such that an assembly of atoms, when randomly placed there, would have an equal probability of forming the reactants or of forming the products of that elementary reaction.*

The role of Gibbs energy (or free energy more generally) is discussed below, but here the significant and useful concept to be noted is that the transition state has an equal probability of forming either the reactants or products of a one-step reaction that has no reaction intermediate. The transition state is not identified with a single structure but rather with a "set of states" (where "states" should be understood as "microstates") or with an ensemble of configurations each comprising an assembly of atoms possessing a particular geometry and energy. In contrast to the expanded entry in the 1994 version of the *Glossary*,<sup>23</sup> the transition state is not to be identified with a species 'characterized by one and only one imaginary frequency': that feature is the characteristic of a transition structure corresponding to a saddle point on a PES (see above).

Derivations of the TST rate expression assume the separation of nuclear and electronic motions and a Maxwell-Boltzmann distribution of states among the reactant molecules, along with the following assumptions unique to TST: (i) molecular systems that pass through the transition state towards products cannot turn round and return to reactants (non-recrossing assumption); (ii) motion along the reaction coordinate through the transition state (i.e. along the transition vector) is separable from other motions and can be treated classically as a translation; (iii) the Maxwell-Boltzmann distribution of states also applies



to the transition state.<sup>9</sup> A dividing surface can be defined, orthogonal to the minimum-energy reaction pathway in the vicinity of the saddle point, such that all systems entering from one side must pass through to the other side. The molecular systems passing through the transition state do not all have the same potential energy or velocity, and they do not all follow the minimum-energy reaction path; they may cross the dividing surface at any point, subject only to the condition that having crossed in one direction they do not return. TST derivations usually consider the concentration of systems in a small but finite volume on the dividing surface, but this arbitrary volume disappears from the final TST rate expression, Eq. (1), for a reaction from reactants R to products P, where  $k$  is the rate constant,  $k_B$  is the Boltzmann constant,  $T$  is the absolute temperature,  $\Delta E$  is the potential energy barrier, and  $Q_R$  is the partition function for the reactants. What remains is a transition-state partition function  $Q^\ddagger$  which, for an  $N$ -atomic molecular system, is a product of  $3N - 1$  factors, one for each degree of freedom except that for motion orthogonal to the dividing surface.

$$k_{TST} = \frac{k_B T}{h} \frac{Q^\ddagger}{Q_R} e^{\frac{-\Delta E}{k_B T}} \quad (1)$$

This equation can be recast into an equivalent expression, Eq. (2), in terms of the activation free energy  $\Delta^\ddagger G$ , which is defined as the free energy difference between the transition state (with  $3N - 1$  degrees of freedom) and the reactant state (with  $3N$  degrees of freedom).

$$k_{TST} = \frac{k_B T}{h} e^{\frac{-\Delta^\ddagger G}{k_B T}} \quad (2)$$

The term "transition state" is sometimes misused to refer to any relatively high-energy molecular species occurring in a sequence of elementary reactions between initial reactants and final products; in other words, a reaction intermediate is incorrectly considered as a transition state.<sup>36</sup> Clearly, this misuse should be strongly discouraged. Bauer rightly brought attention to the clear distinction between molecular structures and molecular states, and proposed that "transition state" should be replaced by "critical transition structure";<sup>37</sup> this suggestion has not been adopted and is unnecessary, provided that the distinction between transition state and transition structure is maintained consistently.

## 4. COMPUTATION AND EXPERIMENT FOR SIMPLE SYSTEMS

### 4.1 Application of statistical mechanics to a single transition structure

Within the Born-Oppenheimer approximation, the smoothly varying potential energy for a particular molecular system may exhibit a pair of reactant and product minima linked by a saddle point for an elementary reaction. As noted above, the TST rate expression, Eq. (1), includes the transition-state partition function  $Q^\ddagger$ , but – as also noted above – the transition state is not a single structure but a set of states each comprising an assembly of atoms possessing a particular geometry and energy. How is its partition function to be evaluated? It might be thought that the number of systems actually in the transition state at any instant is too small to be treated statistically, but statistical-mechanical procedures consider the time-averaged flux of systems through the transition state.<sup>8</sup>

Since the power and availability of computer packages for electronic-structure calculations has enabled almost any researcher to determine optimized structures, energies and harmonic vibrational frequencies for energy minima and saddle points on PESs for many reacting systems with relative ease, it is now a straightforward matter to obtain thermodynamic properties for both reactant structures and transition structures. Indeed, it was the development of these techniques of computational chemistry that made it necessary to distinguish a transition structure from a transition state, as described above. However, following the original suggestions of Eyring,<sup>2</sup> Evans and Polanyi,<sup>3</sup> this approach implicitly assumes that the activation barrier  $\Delta E$  is the potential-energy difference between the saddle point and the reactant minimum, and that the transition-state partition function  $Q^\ddagger$  is determined by the geometry and vibrational frequencies of the transition structure alone.

For reactions in the gaseous phase or in a solution where solvent effects are negligible, not only are the energy minima for reactants and products well defined but also the saddle point for each elementary reaction are well defined. Moreover, for each reaction there is a single MERP leading from a single reactant structure to a single product structure by means of a single transition structure. The standard ideal-gas, rigid-rotor and harmonic-oscillator approximations and standard expressions from statistical mechanics are employed for the evaluation of partition functions for separable translational, rotational, and vibrational

motions of each structure corresponding to a stationary point on the PES, with each of these individual species being considered as adequately representative of the whole ensemble of molecular systems in the particular regions of phase space corresponding to reactants, products and transition state. The expression for the translational partition function involves mass, temperature, and a volume which depends upon the chosen standard state of the system; it also assumes that the system is comprised of non-interacting molecules at infinite dilution. The rotational partition function involves temperature and moments of inertia, which are easily obtained for a single optimized equilibrium structure or transition structure. The vibrational partition function involves temperature and the  $3N - 7$  real vibrational frequencies for a transition structure. The partition functions provide the bridge between molecular properties and macroscopic thermodynamic properties of molecular systems.

#### 4.2 Inference of transition-state structure from empirical studies

Mechanistic studies, employing the experimental tools of physical organic chemistry, often yield results that are interpreted as some measure of transition-state structure. For example, the slope of a linear Hammett or extended Brønsted correlation may be considered as reporting on the change in effective charge at the reaction centre between the reactant and the transition state.<sup>38</sup> Kinetic isotope effects (KIEs) have proved to be very useful as probes for bonding changes associated with different sites of isotopic substitution in a reacting molecule because they do not alter the PES of the reacting system, and their use in the elucidation of transition-state structure was well described in the now-classic 1978 book *Transition States for Biochemical Processes* edited by Gandour and Schowen.<sup>34</sup> A powerful combination of experiment and computation was utilized by Schowen and co-workers to deduce transition-state bond orders for the making and breaking bonds for  $S_N2$  methyl transfer in solution and catalysed by an enzyme. Experimental values for primary  $^{13}\text{C}$  and secondary  $^2\text{H}$  KIEs, together with their uncertainties, were plotted onto contour maps of constant KIE computed as parametric functions of the two bond orders, using bond-energy/bond-order approximations. This enabled a range of transition-state structures to be delineated that were consistent with each KIE, and superimposition of the two maps generated smaller ranges of possible structures that were consistent with the observed KIEs for both the catalyzed and uncatalyzed reactions and separately for a model reaction in solution. These results indicated that the partial bond orders between the transferring methyl group and the nucleophile and nucleofuge, respectively, might be significantly larger in the transition-state structure for the enzyme-catalysed reaction than for the uncatalysed reaction.<sup>39</sup> This approach was later formalised by Berti and Schramm<sup>40</sup> as the 'structure interpolation method'. Manual adjustment of bond-order parameters to give a transition-state structure yielding calculated KIEs that agree with experimental values is not only laborious but also error-prone and unable to predict possible alternative structures. A systematic procedure to explore many transition-state structures within the reaction space was first demonstrated by Sims and co-workers for a non-enzymic reaction,<sup>41</sup> but Berti and Schramm's protocol used either X-ray crystal structures or QM optimised structures for the reactant structure and transition-state structure, and interpolations in all the internal coordinates are made without recourse to the empirical relationships used in the earlier work. However, it should be noted that transition-state structures derived in this manner by interpolation are generally not stationary points on a PES and so, even if they possess a single imaginary frequency, strictly they may not be true transition structures. Schramm and co-workers have published many impressive examples of "transition state analyses" for enzymic reactions, based on a combination of experimental KIEs for multiple isotopic substitutions and gas-phase QM calculations: for example, for hydrolysis of thymidine by catalysed by human thymidine phosphorylase.<sup>42</sup> Moreover, these methods have provided valuable insight concerning transition-state structure leading, for example, to successful design of transition-state-analogue enzyme inhibitors as potential drugs.<sup>43</sup>

#### 4.3 Complications: saddle points in series and in parallel - virtual transition states

There are many instances of chemical reactions for which the rate is determined by a number of contributing transition states, either in series along a multi-step pathway or in parallel for competing reaction pathways. In these cases, transition-state structures inferred from observed kinetic parameters do not describe any one of these contributing transition states but rather a weighted average of them, sometimes called a virtual transition-state structure.<sup>44</sup> Schowen suggested that a virtual transition-state

structure is an imaginary species represented as an average of real transition states, in contrast to the picture of a resonance hybrid as being a real structure represented as an average of imaginary structures.<sup>44</sup> Importantly, a virtual transition-state structure derived from, say, experimental KIEs could be used to make predictions about how the reaction rate would respond to other variables such as temperature, pressure, solvent, *etc.*, since this response would also be a weighted-average response from all of the contributing transition states. However, there is a problem in knowing whether an empirically derived transition-state structure corresponds to a "pure" or to a virtual transition state; one technique for discriminating between these two possibilities is based on KIEs for three isotopes of the same element (often protium, deuterium and tritium)<sup>45</sup> In the event of two reaction pathways leading to the same product, an observed KIE would be dominated by the contribution from the transition state of lower energy. In contrast, for reactions involving multiple steps in series, it is the transition state of highest energy that contributes most to an observed KIE.<sup>46</sup> Examples of this type of behaviour in enzyme-catalysed ester hydrolysis have been discussed by Quinn.<sup>47</sup> The point of this in the present context is to note that observed kinetic parameters do not necessarily have a simple correspondence to a single transition state, let alone a single transition structure, and that in these circumstances a transition-state structure inferred from experimental observations is not a real physical entity. For  $P$  multiple reaction pathways in parallel, the apparent Gibbs energy of activation  $\Delta^\ddagger G_{\text{app}}$  derived from experiment is given by Eq. (3), with  $s = -1$ , and is smaller than any of the values  $\Delta^\ddagger G_i$  for reaction through each of the individual transition states  $i = 1$  to  $P$  relative to the same reactant state.

$$\Delta^\ddagger G_{\text{app}} = RT \ln \left\{ \sum_i^P \exp \left[ (s) \Delta^\ddagger G_i / RT \right] \right\} \quad (3)$$

For  $P$  multiple reaction steps in series, the apparent Gibbs energy of activation  $\Delta^\ddagger G_{\text{app}}$  derived from experiment is also given by Eq. (3), but with  $s = +1$ , and is larger than any of the values  $\Delta^\ddagger G_i$  for each of single transition states  $i = 1$  to  $P$  relative to the same reactant state.<sup>44</sup>

An instructive example of transition structures both in series and in parallel is provided by a computational study of the identity displacement of protonated *t*-butanol in water.<sup>48</sup> The  $\text{O}_{\text{nu}} \cdots \text{C}$  and  $\text{C} \cdots \text{O}_{\text{lg}}$  distances from  $\text{C}_{\text{B}}$  to the nucleophile and nucleofuge O atoms, respectively, optimized by means of the HF/6-31G\* method with the polarized continuum model (PCM) for aqueous solvation (Fig. 3) clearly show concerted making and breaking of these bonds consistent with an  $\text{S}_{\text{N}}2$  mechanism with a potential energy barrier of about 81 kJ mol<sup>-1</sup>. However, instead of a single transition structure with a transition vector involving asymmetric  $\text{O}_{\text{nu}} \cdots \text{C} / \text{C} \cdots \text{O}_{\text{lg}}$  stretching coupled with Walden inversion about  $\text{C}_{\text{B}}$ , a sequence of three transition structures in series is found at this level of electronic structure theory, each of which corresponds to internal rotation of one methyl group. It is essential for these methyl-group rotations to occur somewhere along the reaction pathway or else Walden inversion would lead to a product complex with each methyl group eclipsed with the C–O bond; however, simultaneous rotation of all three groups leads to a higher-order saddle point, i.e. to a hill-top structure. Inspection of any one of the three individual transition structures does not reveal that the overall reaction is nucleophilic substitution: one cannot see the wood for the trees. The picture is yet more complicated for several reasons. Of course, the process can be initiated by rotation of any one of the three methyl groups, and this may occur in either a clockwise or anti-clockwise direction. Thus, for rotation of methyl group 1 (as labelled in Fig. 3) in the first step from reactant complex RC to intermediate  $\text{INT}_1$ , there are two enantiomeric transition structures  $\text{TS}_1$  and  $\text{TS}_1'$  in parallel. Equivalently, the third step, from  $\text{INT}_2$  to the product complex PC by rotation of methyl group 3, involves a pair of enantiomeric transition structures  $\text{TS}_3$  and  $\text{TS}_3'$  in parallel, which are also enantiomerically related to  $\text{TS}_1$  and  $\text{TS}_1'$ . Clockwise or anticlockwise rotation of methyl group 2 leads to one and the same  $\text{TS}_2$ . However, steps 2 and 3 could, with equal probability, involve rotation of methyl group 3 followed by methyl group 2, meaning that there are also parallel pathways for step 2.

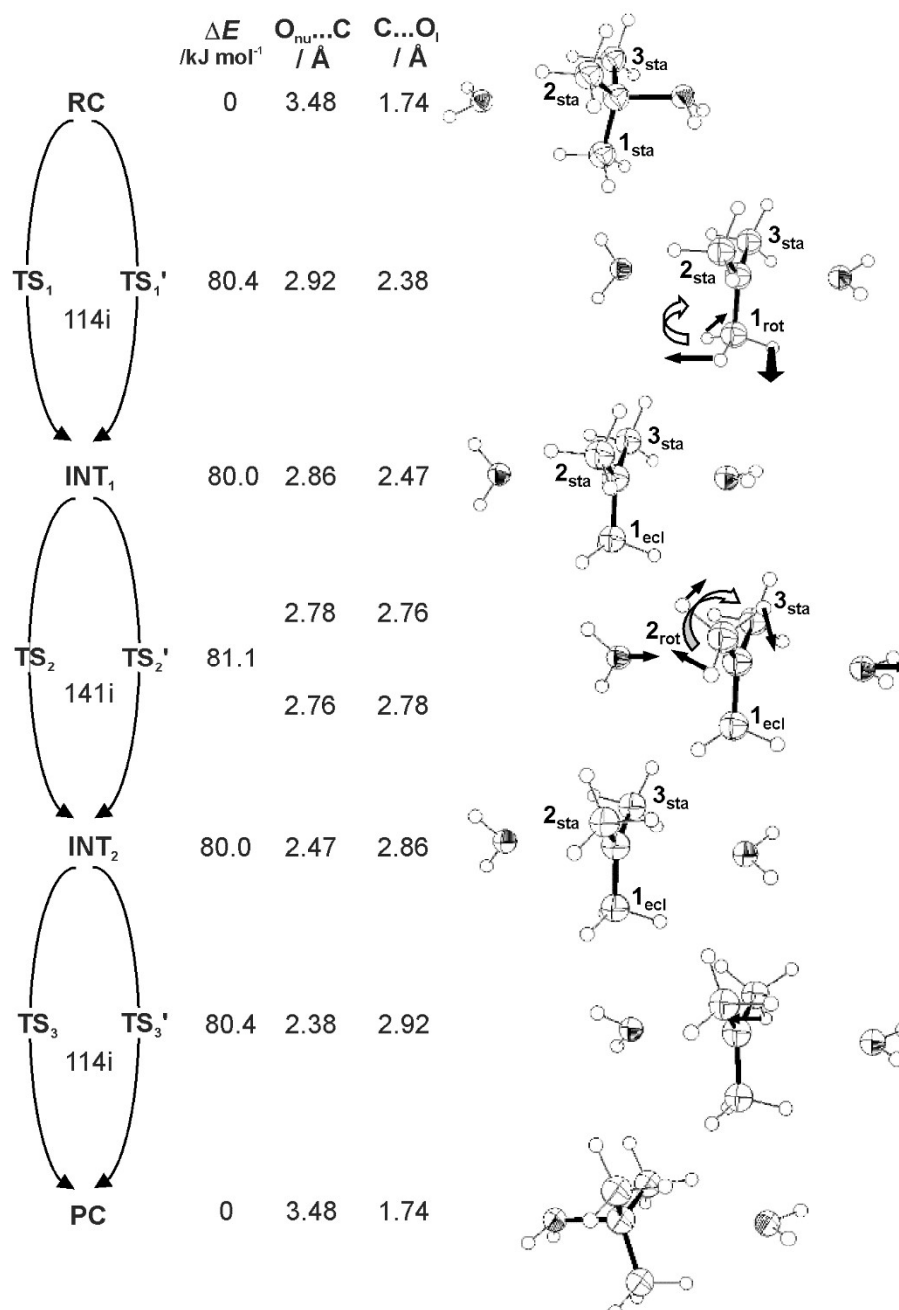


Fig. 3 Stationary structures on HF/6-31G\*/PCM(water) potential energy surface for identity displacement of protonated *t*-butanol in water.

It is entirely likely that a different choice of QM method or treatment of solvation would affect the topography of the PES in the example just discussed, but the point being made here is that, even in apparently simple systems involving only a small number of atoms, it is possible to obtain surprisingly complex patterns of multiple transition structures and reaction paths which may confound simplistic attempts to apply TST to a single reactant structure and single transition structure computed by means of a standard package. There is no simple correspondence between a transition structure and the transition state.

It is common occurrence that there exist multiple conformations of a reacting molecule and also multiple conformations of transition structures for that reaction. For example, hydrogen-atom abstraction by the hydroperoxy radical from any of the methyl groups in *t*-butanol involves 46 independent reaction paths.<sup>49</sup> Several "multi-conformer" TST methods have been proposed,<sup>50,51,52</sup> to deal with the situation in which each of many reactant-structure conformations may react by multiple parallel paths corresponding to different transition-structure conformations. A generalization of the Winstein-Holness equation (for two reactant conformers each associated with a single transition state) involves summation of mole-fraction-

weighted conformer-specific rate constants for reaction through each individual transition-state conformer,<sup>53</sup> and this is equivalent to the scheme described above for parallel pathways in which the Gibbs energy of activation for each individual transition state is taken with respect to the lowest-energy reactant-state conformer. It was noted long ago<sup>54</sup> as well as again recently,<sup>55</sup> however, that in TST it is not possible to associate a given transition-state conformer with a unique path originating from a specific reactant conformer: provided that rapid equilibrium exists between all reactant species separated by low-energy barriers, then any transition structure may be reached from any reactant structure. In this situation there is a plethora of possible elementary steps, each with its own IRC path.

#### 4.4. Potential energy vs. free energy

At the 1962 Chemical Society meeting in Sheffield on 'The Transition State', Porter commented that 'potential-energy and free-energy are used rather indiscriminately to define the transition state';<sup>56</sup> in response, Szwarc pointed out that: (i) whereas potential energy is a mechanical concept, free energy is a statistical-mechanical concept; (ii) the potential-energy and free-energy maxima along the same reaction path need not coincide.<sup>57</sup> These points were discussed by Laidler, who noted that there is free and spontaneous motion for individual molecules from the top of a potential-energy barrier towards either reactants or products but that 'we are not dealing [in TST] with individual molecules but with an assembly of molecules in a statistical distribution among energy states'.<sup>58</sup> The possibility of spontaneous motion for such a statistical distribution (at  $T > 0$  K) is governed by free energy and not by potential energy. While the fate of a single molecule can be determined from the forces acting on it, the evolution of an assembly of molecules depends on the mean force acting on the statistical distribution. Instantaneous forces are given by the gradient of the molecular potential energy, which, in the framework of the Born-Oppenheimer approximation, is a function of the nuclear coordinates alone; potential energy is the energy possessed by a system by virtue of its position alone. Analogously, the mean force can be obtained from the gradient of an associated potential, known as the potential of mean force (PMF),<sup>59</sup> equivalent to the free energy.

The free energy is a property associated with thermodynamic states, and involves temperature because it depends not only on the position of each particle in a system but also on their momenta. It gives information about the relative probability of finding the system in a particular state (e.g. reactant state, product state or transition state) and so determines the composition at equilibrium (from the free energy difference between products and reactants) and, through the use of TST, the kinetics of the process (from the free energy between the transition state and the reactants). Thus a free energy change provides a direct connection between computation and experiment. From a molecular perspective, this property can be obtained using statistical mechanics by averaging over all possible values of not only the positional coordinates  $q$  but also the conjugate momenta  $p$ . This is achieved by integrating over all degrees of freedom in phase space for the state of interest:  $3N$  coordinates and  $3N$  momenta for reactant and products states but only  $3N - 1$  coordinates and  $3N - 1$  momenta for a transition state,<sup>60</sup> as given by Eq. (4) for the Helmholtz energy  $A$ .

$$A = -k_B T \ln Q = -k_B T \ln \frac{1}{h^{3N}} \int e^{\frac{-E(q^{3N}, p^{3N})}{k_B T}} dq^{3N} dp^{3N} \quad (4)$$

where  $E(q^{3N}, p^{3N})$  is the total energy of the system (kinetic and potential) corresponding to all the possible combinations of coordinates and momenta for the state of interest (reactants, products and transition state).

The dependence or variation of the free energy with respect to a selected coordinate can be made explicit if the integration above is carried out for all the variables except for the one of interest. The resultant magnitude is the PMF, from which the mean force acting on that coordinate can be derived; a free-energy profile may be obtained by following the change in magnitude of the PMF as a function of the selected coordinate. This concept can be generalized to more than one coordinate, giving rise a multidimensional PMF or free-energy surface (FES). While the free energy is related to the probability of a macroscopic state, the PMF or FES provides the probability of finding the system with particular values of the selected coordinates, independently of the values taken by the rest of coordinates and momenta of the system. As said before, its gradient gives the mean force acting on a system in a statistical distribution and 'the question of whether or not there is spontaneous motion for such a statistical distribution is determined by the free energy and not by the potential energy'.<sup>58</sup>

It is worth emphasizing that the molecular partition functions  $Q$  appearing in Eq. (1) depend on the  $3N$  (or  $3N - 1$ ) degrees of freedom of the  $N$  atoms of an individual molecule in configurational space which is considered as representative of all molecules in the system. In contrast, Eq. (4) does not involve individual molecular partition functions, but considers all atoms of the whole molecular system in phase space. The distinction should become clearer in the discussion of condensed systems in the next section.

Finally, Laidler noted that it is more fruitful to think in terms of free energy than potential energy for unimolecular homolysis (e.g. dissociation of ethane to form methyl radicals) for which there is no maximum in the potential-energy profile along the breaking C–C bond<sup>58</sup> and no transition structure corresponding to a saddle point on a PES. An increase in entropy with elongation of the bond may cause a maximum to appear in the free-energy profile at a given temperature, due to loosening of vibrational modes, and thereby may generate a transition state.

## 5. TRANSITION STATE FOR CONDENSED SYSTEMS: CONCEPTS AND SIMULATIONS

### 5.1. Free-energy surfaces for condensed systems

In the examples discussed above, the statistical distribution of reactant molecules can be obtained using a single representative structure, for example a minimum on the PES, neglecting interatomic interactions and by assuming simple models such as the rigid-rotor and harmonic-oscillator approximations for the distribution of energy states. As explained before, these models provide analytical expressions for the partition functions, from which the free energy can be derived by means of Eq. (4). It is worthwhile to pause here to note that the expressions for the partition functions that are usually provided in textbooks correspond to a canonical distribution: this is the distribution obtained when the number of particles, the volume and the temperature of the system are fixed. In such a case the previous expression provides the Helmholtz energy and not the Gibbs energy, despite the latter being more commonly used in chemistry. However, the numerical difference between these two quantities is chemically irrelevant for processes taking place in condensed phases.

In the case of molecular systems in condensed phases, such as solutions, biomolecules or solids, the free energy of a system cannot be obtained from the partition function. Such a system contains a large number of degrees of freedom which are coupled because of the presence of intermolecular interactions. The resulting PES is typically very rugged, containing a large number of stationary structures, and leads to vibrational motions that are distinctly anharmonic. In these cases, computational simulations offer the only reliable way to access to free-energy variations associated with conformational or chemical changes. For example, in molecular dynamics (MD) simulations the configurational space of a system is explored by means of solving Newton's equations of motion. The free-energy change associated with a particular transformation between two thermodynamic states of a system may be obtained from the relative probability of finding the system in each of these states during the course of the simulation, i.e. by counting the number of times that each of these states appears during the simulation. The larger the probability of a state the lower its free energy. Similarly, the PMF or free-energy profile along a particular coordinate of a system is related to the probability of finding the system at different values of the coordinate under analysis and then a simple counting of the number of times that a given value of the coordinate appears during the simulation could give us the probability, and thus the free-energy profile, for this coordinate. Moreover, if this coordinate is the reaction coordinate, then one can obtain the reaction free-energy profile and the free-energy difference between products and reactants (that determines the chemical equilibrium) and between the transition state and reactants (that determines the chemical kinetics).

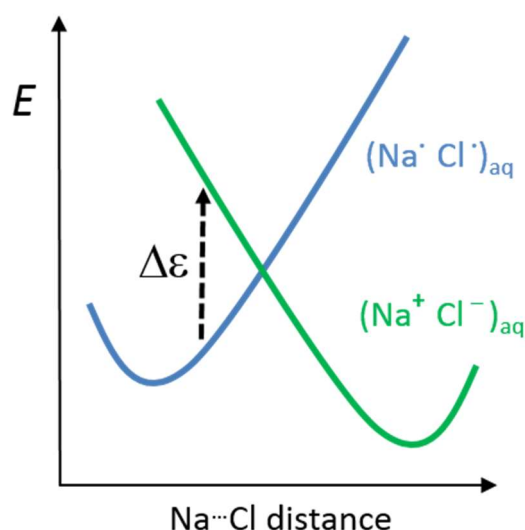
This idea can be generalized to more than one coordinate. For example, a 2D free-energy surface (FES) can be obtained from the probability of finding the system presenting two particular values of the selected coordinates. However, a consequence of the fact that chemical reactions involve free-energy differences larger than the thermal energy ( $k_B T$ ), is that finite-length MD simulations of the system do not adequately sample all values of the selected coordinate in order to provide statistically reliable free-energy differences: only those values associated with low energy are explored sufficiently even in long simulations. In practice, the transition-state region would never be sufficiently explored and so its probability relative to that of the reactants cannot be determined by means of direct MD simulations. However, low-probability configurations of the system with special interest, such as the transition state, can be explored using enhanced sampling techniques, such as umbrella sampling<sup>61</sup> or metadynamics.<sup>62</sup> In these techniques biasing

potentials are applied to force the system to visit the desired values of the selected coordinate(s), thereby increasing the probability of visiting high-energy regions. The reader is referred to specific reviews on free-energy methods to learn about recent advances in the field.<sup>63</sup>

## 5.2. Collective Variables

The FES is a valuable tool with which to explore chemical reactivity in condensed phases. It can tell us the probability of finding the system at the transition state or, in other words, what is the value of the activation free energy that, in turn, determines the reaction rate constant via Eq. (2). Obviously, this requires the selection of an appropriate set of coordinates with which to build the FES via the sampling obtained from computational simulations. The selection of adequate coordinates with which to trace the FES is a far from trivial matter. An incomplete selection of coordinates can lead to activation free energies that are too small, because not all the changes needed to produce the reaction under study are being considered. On the other hand, an incomplete set of coordinates can also produce discontinuity problems in the sampling by means of the umbrella-sampling or metadynamics methods, which lead to activation free energies that are too high.<sup>64</sup> Since the computational cost for calculation of a free energy hypersurface increases exponentially with the number of coordinates, this problem cannot be solved simply by increasing continuously the number of coordinates to be explored but instead by carefully selecting the coordinates that are employed in the construction of the FES.

In condensed phases, one can often find the situation where a reaction process is driven by a collective motion. A typical example is the dissociation of sodium chloride in aqueous solution.<sup>65</sup> In the gas phase the process can be perfectly controlled by the interatomic distance: this distance is *the* reaction coordinate. However, the process is much more complex in aqueous solution. The increase of the distance between the two atomic centers is accompanied by a separation of charges due to the formation of the corresponding ions. This charge separation must be stabilized by solvent molecules, which must be reoriented in order to align their dipoles with the electric field created by the ions. If that did not happen the dissociation would be unsuccessful. The process of reorientation of water molecules is a collective motion, i.e. one that involves many atomic Cartesian coordinates, and thus must be described using collective variables. Examples of collective variables that have been used to obtain FESs include: coordination numbers for the description of protein conformational changes<sup>66</sup> or sodium chloride dissociation,<sup>67</sup> the number of intramolecular hydrogen bonds for protein folding,<sup>68</sup> the hybridization change to describe hydride transfer between  $sp^2$  and  $sp^3$  carbon atoms,<sup>69</sup> the root-mean-squared deviation with respect to a reference structure for loop motions in proteins<sup>70</sup> or the electrostatic potential created on a particular atomic center to describe environmental changes during chemical reactions in aqueous solution or enzymes.<sup>71</sup> These collective variables can be used in combination with valence coordinates (bond lengths, valence angles and torsional angles) to obtain FESs for chemical reactions in condensed phases. Another collective variable is the energy-gap coordinate  $\Delta\varepsilon$ , which measures the energy difference between two diabatic electronic states corresponding to reactants and products.<sup>72</sup> In the case of sodium chloride dissociation these states would correspond to the neutral and ionic pairs, as illustrated in Fig. 4. The energy gap depends on all the degrees of freedom of the system: not only the distance between the sodium and chloride centers but also of the disposition of solvent molecules, and so provides, in principle, a more complete picture of the chemical process in a single coordinate. When the coordinate takes the value  $\Delta\varepsilon = 0$  both diabatic states have equal energy, and this defines the position of the transition state. As said, the main advantage of this coordinate is that it includes all the rearrangements needed for a particular chemical reaction. The main drawback of the coordinate is that it relies on a valence-bond description of the electronic structure<sup>73</sup> while the majority of studies on chemical reactivity make use of a molecular-orbital picture.



**Fig. 4** The energy gap coordinate  $\Delta\epsilon$  for NaCl dissociation in aqueous solution.

### 5.3. Minimum Free-Energy Paths

The use of collective variables can alleviate the problem associated with the computational cost of the construction of multidimensional FESs. One single coordinate can be used to follow the evolution of many atoms or molecules during a chemical reaction reducing the dimensionality of the FES. However, the use of collective variables does not guarantee that the dimensionality of the FES associated with a particular chemical reaction can be reduced enough to result in an affordable computational effort. Chemical reactions involving several component processes, for example when one or more proton transfers are required to activate a nucleophile or/and a leaving group, may require the construction of multidimensional FESs to discern all the features of the process under analysis.

Another strategy to reduce the computational cost consists in focusing effort on only the most interesting regions of the FES. Since during a chemical reaction most of the reactive trajectories take place within a small "tube" around the minimum free energy path (MFEP),<sup>74</sup> it is unnecessary to explore other regions of the multidimensional FES (see Fig. 5). The MFEP is the generalization of the MERP, defined above, but traced on the FES instead of the PES, and it provides the path with lowest free energy connecting reactants and products. There are different computational strategies to determine the MFEP or similar pathways,<sup>75</sup> but the string method is one of the most commonly used.<sup>76</sup> One of the advantages of these methods is that their computational cost is, in principle, independent of the number of coordinates chosen to define the FES. For example, Hammes-Schiffer and coworkers used the string method to study the self-cleavage reaction mechanism in *glmS* ribozyme.<sup>77</sup> The reaction involves the attack of an activated O2' hydroxyl group to the phosphate group to break the P-O5' bond with the next nucleoside. The MFEP was traced on a FES defined by 12 coordinates that included the distances of the phosphorus atom to the leaving group and the nucleophile, as well as the distances associated to all possible proton transfers involved in the activation of the nucleophile and of the leaving group. Another advantage of the use of free-energy path methods is that the progress along the MFEP, which would be equivalent to the progress along the MREP discussed in section 3.4, is the best possible reaction coordinate that can be defined within the subspace used to construct the FES,<sup>78</sup> completing the parallelism between MFEP and MREP.



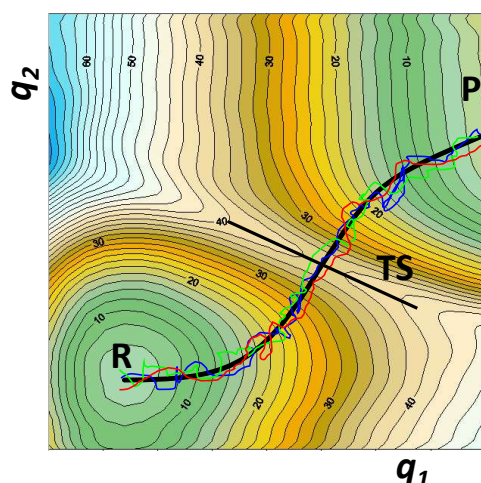


Fig. 5 Reaction tube: most of the reactive trajectories (thin colored lines) take place around the minimum free-energy path (thick black line) across a (schematic) 2D FES obtained as a function of two coordinates  $q_1$  and  $q_2$ . Relative energy contours are colored from green (low) to blue (high). **R**, **P** and **TS** indicates the regions corresponding to reactants, products and transition state.

#### 5.4. Variational Transition State Theory

As we have discussed above, conventional TST provides a recipe to define the transition state from a knowledge of the PES. The transition state is formed by the set of microscopic states found on a hypersurface, the dividing surface, placed at the saddle point and orthogonal to the MREP. The question now is, how can we define the transition state on a FES?

An important feature of TST is that, because of the non-recrossing assumption, this theory always overestimates the value of the rate constant. For this reason, among all possible definitions of the transition state, the best candidate should be the one yielding the lowest possible value for the rate constant or, according to Eq. (2), the maximum value for the activation free energy. This choice would lead to a dividing surface with the minimum number of recrossing trajectories. Several types of recrossing trajectory are shown in Fig 6a: some may start on the reactant side of a barrier but return before reaching the product-side energy-minimum; some may do the reverse, finishing on the product side from where they originated; others may traverse the barrier more than once. Thus, a variational optimization can be applied to the rate constant, resulting in the variational transition state theory (VTST).<sup>79,80,81,82</sup> In VTST the transition state is generalized to be an arbitrary hypersurface in the phase space dividing reactants from products. The best possible transition state may be found varying the position and orientation of the dividing surface in order to minimize the reaction rate or maximize the activation free energy. This means that for a given reaction coordinate, the position of the transition state will correspond to the maximum of the free energy profile along that coordinate, as illustrated by Fig 6b. Firstly, suppose that the value of coordinate  $q_1$ , the initially assumed reaction coordinate, at the maximum of a potential-energy profile is as given by the vertical gray line labelled **TS1**: it might be that few or even no trajectories originating from the reactant minimum **R** on the FES actually reach the product minimum **P**. Re-positioning the dividing surface to a different value of  $q_1$ , at the free-energy maximum as marked by the vertical black line labelled as **TS2**, may reduce the number of recrossings and allow more trajectories to cross successfully from **R** to **P**. Secondly, since for processes in condensed phases the definition of a good reaction coordinate is non-

trivial, the reaction coordinate itself can be optimized in order to maximize the activation free energy. Selection of an incomplete reaction coordinate means that part of the work needed to arrive to the transition state is missed, causing the activation energy to be too low and the rate constant to be too large. However, improving the definition of the reaction coordinate by inclusion of all the relevant degrees of freedom, allows the number of recrossing trajectories to be reduced significantly, raising the activation free energy and decreasing the rate constant. This is illustrated in Fig. 6b: re-orienting the dividing surface from the vertical gray line (**TS2**) to the rotated red line labelled **TS3**, which minimizes the recrossing trajectories, and corresponds to the reaction coordinate being changed from  $q_1$  alone to the best possible linear combination of  $q_1$  and  $q_2$ . It may appear obvious, from inspection of Fig. 6b, that TS3 is the best transition state, since the red line denoting the dividing surface not only passes through the saddle point on the FES but also runs along the ridge separating the reactant and product free-energy basins. But if the correct position and orientation of the best dividing surface is not known in advance, then the best reaction coordinate cannot be determined. This problem for FESs is analogous to that for PESs described in section 3.4.

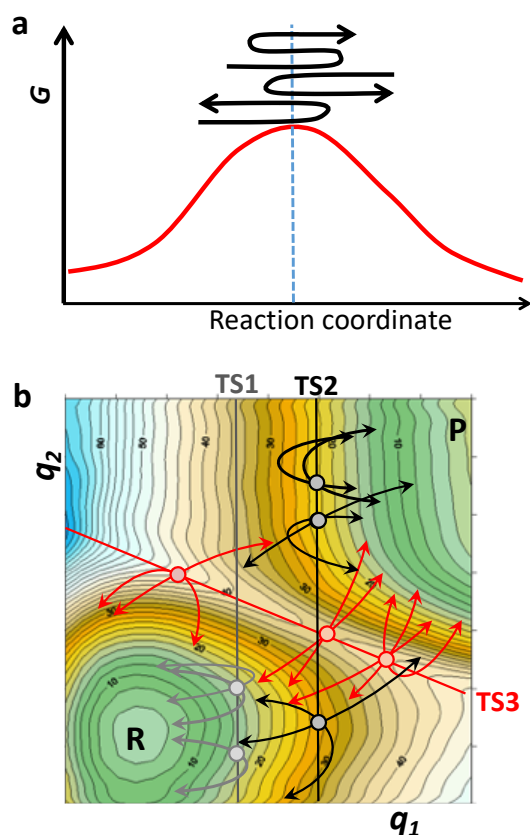


Fig 6. (a) Types of recrossing trajectories. (b) Representation of a FES for a reaction process as a function of two collective variables (CV1 and CV2). The best candidate for a dividing surface in TST is that one minimizing the error due to the non-recrossing assumption. This can be achieved optimizing the position of the dividing surface along a given reaction coordinate (as made from **TS1** to **TS2**, where the reaction coordinate is assumed to coincide with  $q_1$ ) or optimizing the reaction coordinate itself (as made from **TS2** to **TS3**, where the reaction coordinate is obtained as a linear combination of  $q_1$  and  $q_2$ ).

A nice example of the use of the variational principle to optimize the definition of the transition state is illustrated by the work carried out by Hummer and coworkers on the catalytic cleavage of the RNA backbone of RNase H.<sup>63</sup> The reaction was analysed by constructing a FES as a function of two coordinates, and then the best possible transition state on that 2D surface was obtained by looking for the linear

combination of coordinates that maximized the activation free energy. This idea has been generalized in a method to look for the best linear combination of an arbitrary number of coordinates to define the dividing surface. The position and orientation of such a dividing surface (or hyperplane) is defined as a linear combination of collective variables that can be optimized using the variational principle. This strategy was used to find the best possible transition state in a subspace of up to 18 coordinates for the enzymatic transformation catalysed by isochorismate pyruvate lyase.<sup>66</sup>

### 5.5. Transmission Coefficient

As described above, VTST provides a way to optimize the transition state. For practical reasons, in realistic simulations of chemical processes in condensed phases, this optimization must be carried out in a subspace of the coordinates rather than in the complete phase-space of the system, leading inevitably to an incomplete definition of the transition state. Since, in practical cases, TST always overestimates the rate, the quality of a transition state for a given reaction can be assessed by the corresponding TST rate constant: the better the transition state the smaller the value of the rate constant given by TST. A convenient way to consider this is to introduce a transmission coefficient  $\kappa$  that relates the TST rate constant to the exact one, Eq. (5).

$$k = \kappa \cdot k_{TST} \quad (5)$$

The value of  $\kappa$  corresponds to the fraction of flux of systems crossing the dividing surface which indeed is reactive, i.e. which actually leads to products. In classical mechanics, if the transition state were optimized in the complete phase-space, the non-recrossing assumption would be valid and the TST value of the rate constant would be exact; in that case  $\kappa = 1$ . Otherwise, for any practical definition of the transition state, the dividing surface is recrossed, TST overestimates the rate constant, and  $\kappa < 1$ . There are different kinds of recrossing trajectories that cause overestimation of the TST rate constant and thus a lower value for the transmission coefficient (Fig. 6b). Some trajectories start on the side of the reactants and cross the dividing surface but then turn back from the side of the products; some others do the same thing but starting from the side of the products; and finally, there are reactive trajectories that cross the dividing surface more than once.

The transmission coefficient  $\kappa$  can be evaluated by consideration of many free trajectories, each starting at a point in the selected dividing surface: it is the ratio between the reactive flux and the total flux that crosses the surface.<sup>83</sup> Alternatively, within certain approximations, it can be estimated from the friction exerted on the reacting system by means of fluctuating dynamical interactions with its environment as it advances along the reaction coordinate through the transition state.<sup>84</sup> The evaluation of the transmission coefficient offers a tool by which to assess the quality of a putative transition state for a given reacting system: the higher the value of  $\kappa$  the better the transition state. However, the value of  $\kappa$  itself gives no information about how a putative transition state is wrong: it can be low either because the assumed transition state is not placed at the actual maximum of the free energy profile along a given reaction coordinate, or because the reaction coordinate itself is not good enough (see Fig. 6). In addition,  $\kappa$  may deviate from unity not only due to a suboptimal choice of the transition state but also due to limitations of the TST itself, as discussed below. For reasonable choices of the reaction coordinate, the transmission coefficient for reactions in condensed phases is typically found to lie in the range 0.5-0.9,<sup>80,85,86</sup> which means that the error introduced by TST is typically lower than a factor of 2 (assuming that the potential-energy function used to represent the system is exactly correct).

### 5.6. Reaction coordinate (part 2)

VTST generalizes not only the concept of the transition state but also that of the reaction coordinate. In general, a reaction coordinate is a scalar function of the coordinates of the system (all the coordinates) with has a one-to-one correspondence to the progress of the reaction. When the reaction advances in the direction from reactants to products, the reaction coordinate must increase, and vice versa; an increase in the reaction coordinate means that the system is found at a more advanced position in that direction. The reaction coordinate determines the transition state in the following manner: the transition state is the set of microscopic states found in the dividing hypersurface defined by the value of the reaction coordinate that maximizes the activation free energy.

The suitability of a candidate to serve as an adequate reaction coordinate is often not evident from chemical intuition. For example, in the case of sodium chloride dissociation in aqueous solution, the interatomic distance between the sodium and chloride centers is not a good-enough reaction coordinate. If

the dividing surface is placed at the maximum of the free energy profile along this coordinate the resulting transmission coefficient can be as low as 0.3.<sup>87</sup> While VTST provides a systematic way to improve the definition of both the reaction coordinate and the transition state, there is no guarantee that a non-recrossing dividing surface exists in the configurational space. In such a case, a perfect reaction coordinate could not be defined and an intrinsic error would remain in TST. This error is often denoted as dynamical effects<sup>86,88,89</sup> although this nomenclature can be misleading because TST does include the dynamics of the system, assuming a statistical distribution.

While the transmission coefficient provides a quality test for a putative transition state, a low value is not a sufficient criterion to decide if it is not good enough either because the reaction coordinate is incomplete or because the dividing surface was placed at the wrong position along the reaction coordinate (see Fig. 7). A stricter test on the quality of a transition state is given by the "committor" distribution corresponding to the set of configurations that form the transition state. For each of these configurations the committor is calculated as the probability that trajectories started from that configuration with random velocities (corresponding to a Maxwell-Boltzmann distribution) commits to the products basin. From a hypothetical perfect transition state, all trajectories commit to products in forward time (or conversely to reactants in backward time) without recrossing the dividing surface; in this case TST is exact,  $\kappa = 1$ , and the committor always takes the value 0.5 (Fig. 7a). Systems in condensed phases always present some trajectories that recross the dividing surface, and a good selection of the transition state results in a unimodal committor distribution peaked at 0.5 (Fig. 7b). If the reaction coordinate is good but the transition state has been wrongly placed, for example too close to the reactant state, then the committor distribution is clearly shifted towards 0 (Fig. 7c). If the reaction coordinate is not good enough, then the transition state will contain few structures with an equal probability of ending up in either the reactants basin or the products basin, and the committor distribution present two peaks, close to 0 and 1 (Fig. 7d).

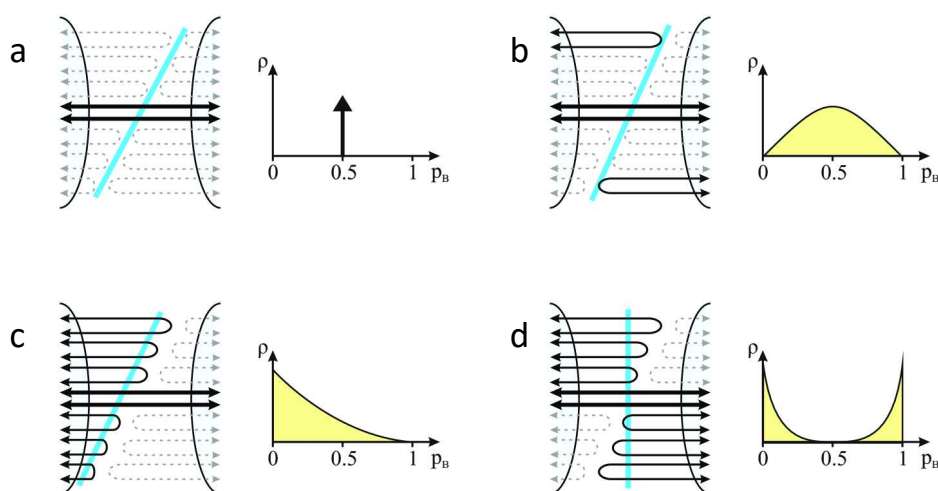


Fig. 7 Different choices of the reaction coordinate and the transition state and the resulting committor distribution.  $p_B$  is the committor and  $p$  its probability density. (a) perfect transition state; (b) good reaction coordinate and good transition state; (c) good reaction coordinate and bad transition state; (d) bad reaction coordinate. Figure taken from ref. 75 and reproduced with permission.

### 5.7. The equicomittor and the error in TST

The committor is in fact the best possible reaction coordinate in the configurational space because its change perfectly matches the reaction advance. The isocommittor surface with value equal to 0.5 (the equicomittor) is the best possible transition state, because all the configurations contained in this ensemble have exactly the same probability to evolve towards either reactants or products. This transition state is sometimes named as the 'stochastic separatrix'.<sup>90</sup> Unfortunately, there is no analytical expression for the committor in realistic systems, so it cannot be directly used as a reaction coordinate in

computational simulations from which the equicommitor could be identified. However, the development of reaction theories that do not rely on the use of a reaction coordinate, such as transition path sampling,<sup>91</sup> in which a Monte-Carlo-like method is used to generate an ensemble of unbiased reactive trajectories, offers a way to generate the equicommitor ensemble corresponding to a given reaction. The properties of the equicommitor can be then used to obtain information about the reaction coordinate, as was done by Schwartz and coworkers in their study of the reaction catalyzed by the human version of the enzyme lactate dehydrogenase.<sup>92</sup>

An interesting property of the equicommitor, or separatrix, is that if an ideal non-recrossing surface exists, for which TST would be exact, this surface must coincide with the equicommitor (Fig. 7a). Conversely, if the equicommitor corresponding to a particular chemical reaction were recrossed, then the "best possible" transition state would be associated with a transmission coefficient less than unity, and TST would give an intrinsic error in the evaluation of the rate constant for that process. For systems with complex nonlinear dynamics, as happens in condensed systems, the equicommitor can indeed be recrossed in practice<sup>93</sup> and analysis of these recrossings provides information about the limitations of TST. In the case of sodium chloride dissociation in aqueous solution, the transmission coefficient corresponding to the equicommitor is  $\sim 0.4$ , and thus TST overestimates the rate constant by a factor of  $\sim 2.5$ . However, this is a difficult case for TST because of the strong coupling of water dynamics with the ion separation and the low activation free energy for dissociation (about  $17 \text{ kJ}\cdot\text{mol}^{-1}$ ). For the enzymatic reaction catalysed by *E. coli* dihydrofolate reductase, which is a more representative case to evaluate the performance of TST in the calculation of the rate constant of chemical reactions, the transmission coefficient obtained for the equicommitor is 0.94, which reduces the error of TST to only 6%, while for the counterpart reaction in aqueous solution the error was of only 14%.<sup>94</sup>

As it has been recently stressed, searching for the best possible dividing surface (and then the best possible reaction coordinate) is not only important to estimate the correct value of the rate constant but also to predict adequately the fate of the system after crossing the transition state.<sup>95</sup> In this sense, recent efforts have been made to optimize transition states with searching methods based in the use of Lagrangian descriptors that are not restricted to the configurational space but consider the whole phase space (coordinates and momenta).<sup>95,96</sup>

## 6. CONCLUDING REMARKS

A recurring theme within the collective consciousness of the physical-organic community appears to be a desire to visualize the transition state. Within the PES-based paradigm of the transition state this desire can be satisfied by a computed transition structure corresponding to a saddle point; these terms are defined and discussed in section 3 above. In section 4, it is argued that there are difficulties in relating this pictorial view directly to experiment, even for supposedly simple systems, and part of this discussion concerns the idea of the virtual TS as an average structure. The discussion of condensed system in section 5, based upon the FES-based paradigm of the transition state, and focussing on the rather abstract concepts of dividing surfaces, equicommitors and separatrices, may aggravate a gnawing desire to "see" the transition state in a more concrete manner. What does "transition-state structure" mean within the context of computational simulations that generate FESs?

There is a fundamental problem with the desire to have a simple, visual picture of the transition state for any chemical reaction: because the transition state is not a single structural entity, any "picture" of it is necessarily an average view.

The view from experiment is inevitably an average view, as obtained for finite timescales and fractions of Avogadro's number. Moreover, the presence of kinetic complexity, and the possibility of numerous transition states either in series or in parallel, means that experiments may yield virtual transition states averaged over numerous "real" transition states that are themselves averages.

The view from computational simulation must also be an average view, obtained from a statistical-mechanical treatment of an ensemble of systems. In the PES paradigm, the partition functions for the reactants, products and transition state of an elementary reaction in an ideal-gas system (with non-interacting molecules) are approximated as simple products of the molecular partition functions of the individual species. However, for condensed systems with significant intermolecular interactions, the partition functions must be obtained by averaging over all accessible microstates in phase space: the probability of any configuration of the system is determined by a Boltzmann factor in which the energy that

appears in the exponent is not the potential energy of an individual molecular species but rather the potential of mean force averaged over the whole system.<sup>59</sup>

Nonetheless, the familiar idea of a chemical reaction taking place by passage of a molecular system over a mountain pass between valleys for reactants and products on an energy surface is still useful, provided that the transition state is not thought of as simply a single structure but rather as a distribution of microstates within a dividing surface passing through the free-energy maximum along the path of lowest free energy between reactants and products (Fig. 8).

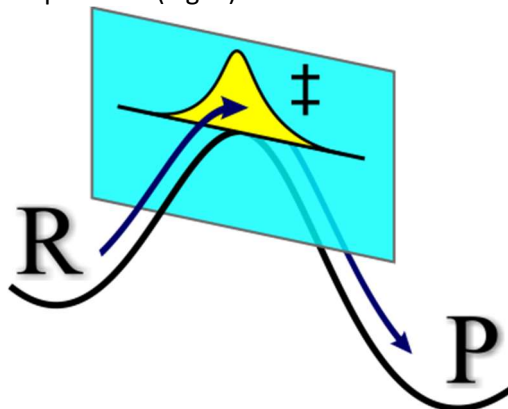


Fig. 8 The transition state as a distribution of microstates (yellow area) within a dividing surface (in pale blue) passing through the free-energy maximum along the path of lowest free energy (black line) between reactants **R** and products **P**.

It is now timely to propose an update to the definition of the transition state from that given previously<sup>35</sup> (subsection 3.10).

*The transition state of an elementary reaction is the ensemble of configurations in the phase space of the whole assembly of atoms that lie on the dividing hypersurface from which there are equal probabilities of the system evolving spontaneously to either reactants or products and which minimises the occurrence of recrossing trajectories.*

To this definition may be added some clarifying comments.

- (i) Defining the transition state as an ensemble of configurations focuses on the coordinates of the system and not on the momenta. From the chemical point of view it is convenient to think in terms of the geometrical arrangements, both of the reacting moieties and of their environment, that are required to produce a particular chemical transformation.
- (ii) The ensemble of configurations that constitutes the transition state depends on the conditions under which the reaction proceeds; for example, the temperature. In TST this ensemble is assumed to be in equilibrium, which facilitates the evaluation of the rate constant at the cost of a (hopefully) small error.
- (iii) The optimal dividing hypersurface is the equicommititor, which minimizes the error due to the non-recrossing assumption in TST. More practical definitions of the dividing hypersurface can be obtained exploring the free energy dependence with a reduced number of variables. In this case the resulting reaction coordinate is necessarily incomplete and the quality of the resulting transition state should be checked by means of computation of the transmission coefficient and the committor distribution. In general, the positioning of the dividing hypersurface along the selected reaction coordinate depends on the temperature, as does the free energy itself.
- (iv) While nuclear quantum effects on the reaction rate can be introduced as corrections to classical TST,<sup>97</sup> or through a quantum version of TST,<sup>98</sup> the impact of these effects on the definition of the reaction coordinate, and thus the nature of the transition state, remain to be investigated.<sup>99</sup> This could be important in the deep-tunneling (low temperature) regime, where most reactive events involve non-

classical motion of light particles (typically hydrogen nuclei) through an energy barrier rather than classical motion over an energy barrier. For reactions in condensed systems at room temperature the impact of nuclear quantum effects on the averaged transition state configuration seems to be small.<sup>100,101</sup>

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